A Phase 2a, Open-label, Pilot Study to Assess the Safety and Efficacy of Psilocybin Administration in Concert with Psychotherapy Among Adult Patients with Fibromyalgia

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Protocol Title: A Phase 2a, Open-label, Pilot Study to Assess the Safety and Efficacy of Psilocybin Administration in Concert with Psychotherapy Among Adult Patients with Fibromyalgia

Compound: TRP-8802

Study Phase: 2a

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Tool Revision History

Version Number: 1.1
Version Date: 12/14/2022
Summary of Revisions Made:

1. Pg 1 Removed Tryp 002 from the title. Added the University of Michigan, Department of Anesthesiology to the sponsor's name and address. Removed header, "Tryp Therapeutics, Inc." Protocol TRYP 002 and signature line. Updated date in the footer.Pg 2, Removed the Investigator's Agreement and signature line.
2. Pg 4-6 Rewrote the Table of Contents – removed EEG
3. Pg 10 Removed TRYP 002 from the protocol tilte and added generic name in the rationale.
4. Pp 12-13, Schedule of assessments: Removed CMSI, Sleep-related Impairment (4a), painDETECT, and PANAS short form (state). Removed PGIC from visits 5-12.
5. Pg 14: Updated typo in subscript e, which read "Error! Reference Source not found".
6. Pg 23: Removed CMSI description.
7. Pg 32: there was a typo of HPPD, which was removed.
8. Pg 41: Removed description of painDETECT, the PANAS, and Sleep-related Impairment scale short form 4a
9. Pg 43: Removed language with the proposed overview of EEG tasks. Also removed language about having electrodes affixed to scalp via electrolyte gel.
10. Pg 44: Removed language in Table 5 to say it is proposed overview of EEG tasks. Also changed time of cap placement given different cap will be used. Removed language on Diffusion tensor imaging as this will no longer be done. Also removed visual stimulus task and post-pain resting EEG (eyes closed) task from Table 6.
11. Pg 45: Modified language in Table 6 to say it is a proposed overview of fMRI task. Also changed resting state fMRI assessment to 20-30 minutes and removed mention to diffusion tensor imaging as this will no longer be done.

Version Number: 1.2
Version Date: 6/2/2023
Summary of Revisions Made:

1. Pg 1 Removed Tryp Therapeutics University of Michigan under sponsor's name and address from the title page and add Kevin Boehnke's name and address. Updated date in footer
2. Section 1.3 – Table 2: Checked off next day monitor forms (V6,7 and V9)

   (F.) Added Breathalyzer performed only on dosing days

   (N.) Wrist Actigraph Day 1 to 14 and Day 50 to 64.
3. Section 4.1.1. Screening: Removed breath alcohol test
4. Section 4.1.5. Removed FM survey and PGI-C at V10, 11, and 12
5. Section 5.2 – Removed "Currently undergoing acceptance and commitment therapy" from the exclusion criteria.

6. Section 8.2.3.3: Noted that participants will wear either the Fitbit Charge 5 or Actiwatch Spectrum.
7. Pg 51: The protocol stated that there would be 20 participants, a holdover from the previous protocol version. Corrected to 10 participants.
8. Pg 66: Corrected typo in the last line of the table, which currently misspells study drug.

Version Number: 1.3
Version Date: 8/23/2023
Summary of Revisions Made:

1. Section 4.1 – Added, "One of the physicians associated with the study will have a brief visit with the study participant during screening or prior to the first dosing session."
2. Section 6.8.1 – Removed "a research pharmacist at the research site will dispense the medication and" from the sentence.
3. Section 10.1.8 - Removed "Definition of what constitutes source data can be found in the Monitoring Plan."
4. Updated date in footer.

Version Number: 1.4
Version Date: 12/05/2023
Summary of Revisions Made:

1. Updated Schedule of assessments to reflect addition of self-pain enmeshment task, self-complexity task, Life events checklist and expectation assessments. Also updated superscripts to reflect these changes on pages 12-14.
2. Page 22: Noted that Life events checklist is now during screening
3. Page 23: Noted that preparation sessions (Visits 3 and 4) can be in-person or virtual.
4. Page 24: Noted that Visit 7 can be in-person or virtual.
5. Page 28: Removed #11. Participants must agree that for 7 days before each TRP-8802 session, he/she will refrain from taking any nonprescription medication, cannabis, nutritional supplement, or herbal supplement except when approved by the Principal Investigator. Exceptions will be evaluated by the Principal Investigator and will include acetaminophen, non-steroidal anti-inflammatory drugs, and common doses of vitamins and minerals.
6. Added Section 8.2.2.5 (self-pain enmeshment), Section 8.2.2.6 (Self-complexity task), Section 8.2.2.7 (expectations assessment) on pages 41-43
7. Page 45: Changed Table 6 to include five, 5-minute resting state fMRI scans (25 minutes total), and edited the tonic cuff fMRI scan into two 5-minutes scans. Also removed evoked pain task. This is now reflected in the text saying, "The fMRI assessment should take a total of approximately 55 minutes to complete and may include any of the assessments included in Table 6."
8. Page 46: Updated text to read "Participants will rest comfortably in the scanner with eyes open for 25 minutes at the beginning of the scan session to obtain baseline measures of

functional brain connectivity. Participants will be asked about current levels of pain intensity, fatigue and anxiety before and after resting state runs. Participants will also undergo two fMRI scans with tonic cuff pressure pain to evaluate functional brain connectivity response to deep pain. Pressure intensity will be set to each participant's Pain 30 to 50 level, as determined during the behavioral visit, and applied for 5 minutes for each scan."
Removed Evoked Pressure Pain task from the imaging tasks from page 47.

Version Number: 1.5
Version Date: 1/10/2024
Summary of Revisions Made:

1. Section 1.3, Page 11: Increased visit window for preparation from +/-3 days to +/-7 days. Also updated screening window from 28 to 42 days. These changes were also made throughout the rest of the document where relevant per tracked changes (e.g., section 4.1.1, Screen period now is -42 days prior to trial initiation).
2. Page 13: Removed the self-complexity task from dosing day, as it should not be performed that day.
3. Page 13: Per protocol, added monitor rating form for Integration visits 10-12.
4. Page 13: Noted that COVID-19 test is performed on dosing days only, as with breath alcohol test.
5. Page 14: Corrected typo in subscript m to read and instead of an.
6. Section 4.1.3, page 23: We note that "one preparatory therapy sessions may occur via a HIPAA-compliant video conferencing platform if necessary."
7. Section 4.1.5: removed language "same two therapists" from this section.
8. Section 5.1, Page 27: Updated inclusion criteria to note that participants must meet "criteria for FM per the 2016 FM survey criteria."
9. Section 5.2, Page 29: Updated language about antidepressant medications
10. Section 6.1.2, page 33: Removed language: "Participants will be expected to be on the research site for at least 8 hours."
11. Page 38: clarified that this is research record rather than medical record.
12. Page 57: Updated SRC language to read: "The SRC will be responsible for the assessment of safety and to make recommendations regarding study progression. The SRC will be composed of the principal investigator, a study therapist, and a study physician. Participant safety, which includes safety signal detection at any time during the study, will be continuously monitored by the SRC. All safety data collected will be summarized and reviewed by the SRC for agreement of next steps."

Version Number: 1.6
Version Date: 2/27/2024
Summary of Revisions Made:

1. Schedule of Assessment: added the +/-7 day window to the preparation sessions.
2. Section 6.1.2, page 32: Added back language: "Participants will be expected to be on the research site for at least 8 hours."

3. Section 1.1, page 10: Updated Safety Review Committee language to “The SRC will be responsible for the assessment of safety and to make recommendations regarding study progression. The SRC will be composed of the principal investigator, a study therapist, and a study physician. Participant safety, which includes safety signal detection at any time during the study, will be continuously monitored by the SRC. All safety data collected will be summarized and reviewed by the SRC for agreement of next steps, which may include:”
4. Section 5, page 30. Removed breathalyzer information from the eligibility criteria 16. This is covered in Lifestyle considerations.
5. Updated dates to 2/27/2024 in footer.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 2a, Open-label, Pilot Study to Assess the Safety and Efficacy of Psilocybin Administration in Concert with Psychotherapy Among Adult Patients with Fibromyalgia

Rationale:

The pressing need for effective fibromyalgia (FM) treatments, the known safety of psilocybin therapy, and the mechanistic plausibility for potential benefit provide a rationale for investigating TRP-8802 (i.e., synthetic psilocybin) therapy as a treatment for FM. An overview of the objectives and endpoints is presented in Table 1. The complete list of study objectives and endpoints is presented in Table 3.

Table 1: Overview of Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety of TRP-8802 under the conditions of this trial	Safety during dosing sessions: vital signs (HR, BP), AEs Safety during trial: AEs
Secondary	
To evaluate the clinical benefit of oral TRP-8802 in concert with psychotherapy to treat chronic pain symptoms in patients with FM	Aggregate weekly worst pain score change from Baseline (Days 1 to 7) to End of Therapy visit (Day 64) on a pain intensity numeric rating scale (PI-NRS) 11-item pain scale
To assess other potential therapeutic effects of TRP-8802 in conjunction with psychotherapy on FM symptoms	Participant self-reported outcomes: • pain interference • sleep • chronic pain acceptance • Patient Global Impression of Change (PGI-C)
Exploratory	
To characterize other TRP-8802 clinical and PD effects	

AEs=adverse events; BP=blood pressure; FM=fibromyalgia; HR=heart rate; PD=pharmacodynamic; PROs=patient reported outcomes.

Note: The aggregate weekly pain score is over a 7-day period.

Overall Design:

Participants with FM and with no exclusionary co-morbid psychiatric disorders are planned for enrollment in the study. This study comprises approximately a 42-day screening period (Days -42 to -1), 3 weeks for baseline and preparation (Days 1 to 18), a 2-dose administration period (Days 22 to 37), integration (Days 43 to 57), the End of Therapy (EOT) visit (Day 64 [with last aggregate worst pain score for the 7 days immediately prior to EOT visit assessed for change from baseline]) and 3- and 6-month follow-up visits (Days 120 and 204).

Brief Summary:

Fibromyalgia is a chronic syndrome of widespread musculoskeletal pain that often manifests with a cluster of co-occurring symptoms, including sleep disturbances, fatigue, cognitive dysfunction, and mood problems including anxiety and depression. Recent studies have provided evidence of altered central pain pathways. Current management of FM typically takes a multidimensional approach including behavioral therapy, exercise, and medication. However, current medications provide only modest benefit and carry significant side effect burden, leading many people with FM to seek other alternatives.

Psilocybin therapy (psilocybin delivered in concert with psychotherapy) may be a safe and effective treatment for symptoms associated with FM. Indeed, psilocybin therapy has shown positive effects in treating cancer-related psychiatric distress, depression, and anxiety; treatment-resistant depression; and nicotine or alcohol addiction. The United States Food and Drug Administration (FDA) has granted Breakthrough Therapy designation for psilocybin in treatment-resistant depression and major depressive disorder. Psilocybin therapy is generally safe and well-tolerated when conducted under controlled conditions. While no clinical studies have explored psychedelic effects among people with FM, a recent review outlined potential mechanisms through which psychedelics could alleviate chronic pain symptoms (Castellanos 2020).

Number of Participants:

Participants will be screened with the goal of 10 participants who will complete both doses of TRP-8802 and the primary and secondary outcome measures and complete the study and follow-up periods.

Intervention Groups and Duration:

This is an open-label study, and participants who meet the inclusion and exclusion criteria will be eligible and invited to enroll. Enrolled participants are planned to receive 2 doses of TRP-8802: a 15 mg dose followed 2 weeks later by a 25 mg dose. The total planned duration of the study for an individual participant from screening to last follow-up is approximately 8 months.

Safety Review Committee:

The SRC will be responsible for the assessment of safety and to make recommendations regarding study progression. The SRC will be composed of the principal investigator, a study therapist, and a study physician. Participant safety, which includes safety signal detection at any

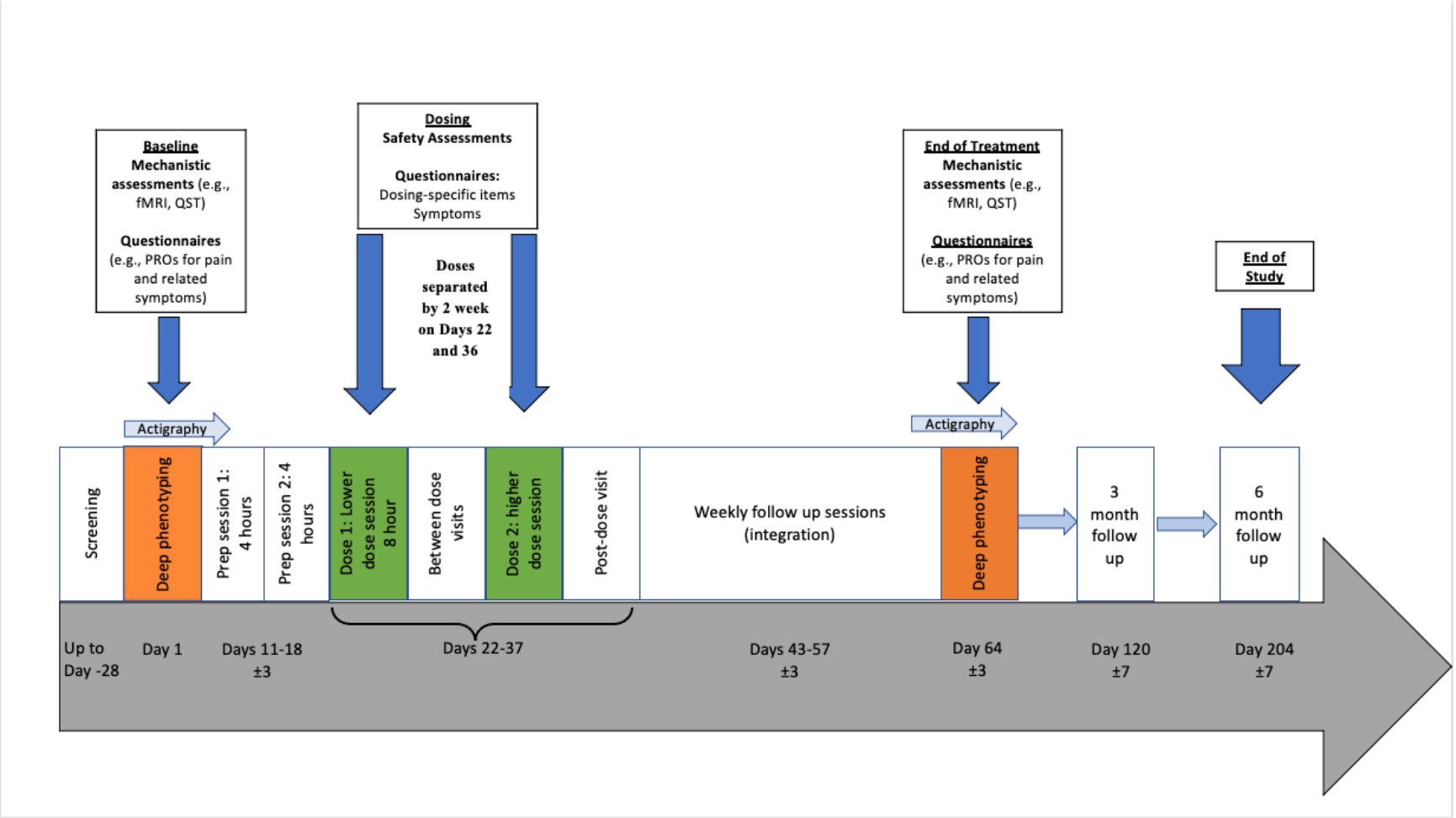
time during the study, will be continuously monitored by the SRC. All safety data collected will be summarized and reviewed by the SRC for agreement of next steps, which may include:

- continue the study as planned
- continue the study with modifications of procedures, such as dose, safety monitoring, or other
- suspend enrollment to further evaluate safety events (mandatory for any event that meets a Stopping Rule [Section 5.5])
- terminate the study

1.2. Schema

A study schema is presented in Figure 1.

Figure 1: Study Schema



fMRI=functional connectivity magnetic resonance imaging; PRO=patient reported outcome; QST=Quantitative Sensory Testing.

1.3. Schedule of Activities

Table 2: Schedule of Activities

Procedures	Screening [a]	Baseline	Preparation	Administration				Integration [b] (2 h)	End of Therapy [c]	Follow-up 3 and 6 months
		Deep Pheno-typing	Therapy	Dose 1 (8 h)	Between Dose 1 & 2 (2 h)	Dose 2 (8 h)	After Dose 2 (2 h)		Deep Pheno-typing	
Visit Number	1	2	3, 4	5	6, 7	8	9	10, 11, and 12	13	14 and 15
Day Number	Up to -42	1 to 7	11 and 18 ±7	22 ±3	23 and 29 ±3	36 ±3	37 ±3	43, 50, and 57 ±3	64 ±3	120 and 204 ±7
Informed consent	X									
Inclusion/ exclusion criteria	X									
• Demographics • Medical history • SCID-5 and SCID-5-PD	X									
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X
Complete blood count and metabolic panel	X									
12-lead electrocardiogram [d]	X									
Pregnancy test for WOCBP [e]	X	X		X		X			X	
Urine drug Breath alcohol test and COVID-19 test [f]	X	X		X		X			X	
PHQ-8 [g] Life events Checklist	X									
Vital signs [h]	X	X		X		X			X	
C-SSRS	X	X	X	X	X	X	X	X	X	X
2016 FM Survey Criteria	X	X							X	X
Expectations assessment		X								

Procedures	Screening [a]	Baseline	Preparation	Administration				Integration [b] (2 h)	End of Therapy [c]	Follow-up 3 and 6 months
		Deep Pheno-typing	Therapy	Dose 1 (8 h)	Between Dose 1 & 2 (2 h)	Dose 2 (8 h)	After Dose 2 (2 h)		Deep Pheno-typing	
Visit Number	1	2	3, 4	5	6, 7	8	9	10, 11, and 12	13	14 and 15
Day Number	Up to -42	1 to 7	11 and 18 ±7	22 ±3	23 and 29 ±3	36 ±3	37 ±3	43, 50, and 57 ±3	64 ±3	120 and 204 ±7
• STOP-Bang		X								
• Sleep Disturbance (8b) • CPAQ-8 • Catastrophizing		X							X	X
PI-NRS daily diary [i]		X	X	X	X	X	X	X	X	
Adverse event reporting [j]		X [k]	X	X	X	X	X	X	X	
• Quantitative sensory test • fMRI		X							X	
Wrist actigraphy [l]		X	X					X	X	
PROMIS-29+2		X		X		X			X	X
Self-enmeshment task		X		X [m]		X [m]			X	
Self-Complexity task		X							X	
TRP-8802 administration				X		X				
Audio/video record of dose				X		X				
Monitor rating form [b]				X	X	X	X	X		
• Mystical Experiences Q30 • Challenging Experiences Q27				X [n]		X [n]				
Psychological Insight Q				X [n]		X [n]			X	X
PGI-C									X	X
Qualitative (written) assessment				X		X				X [o]

Procedures	Screening [a]	Baseline	Preparation	Administration				Integration [b] (2 h)	End of Therapy [c]	Follow-up 3 and 6 months
		Deep Pheno-typing	Therapy	Dose 1 (8 h)	Between Dose 1 & 2 (2 h)	Dose 2 (8 h)	After Dose 2 (2 h)		Deep Pheno-typing	
Visit Number	1	2	3, 4	5	6, 7	8	9	10, 11, and 12	13	14 and 15
Day Number	Up to -42	1 to 7	11 and 18 ±7	22 ±3	23 and 29 ±3	36 ±3	37 ±3	43, 50, and 57 ±3	64 ±3	120 and 204 ±7

AE=adverse event; CPAQ-8=Chronic Pain Acceptance Questionnaire 8; C-SSRS=Columbia Suicide Severity Rating Scale; FM=fibromyalgia; fMRI=functional connectivity magnetic resonance imaging; PGI-C= Patient Global Impression of Change; PI-NRS=pain intensity numeric rating scale; Q=questionnaire; PHQ-8=Patient Health Questionnaire depression scale; PROMIS-29+2=Patient Reported Outcomes Measurement Information System 29-item profile measure plus 2 cognitive functioning items; SAE=serious adverse event; SCID-5=Structured Clinical Interview for Diagnostic and Statistical Manual for Mental Disorders 5th Edition; SCID-5-PD= Structured Clinical Interview for Diagnostic and Statistical Manual for Mental Disorders-5 for Personality Disorders; WOCBP=women of childbearing potential.

Note: Assessments scheduled on a day of study drug administration should be performed prior to study drug dosing unless otherwise specified.

a Informed consent must be obtained before any study-specific screening assessments are performed. Screening assessments are to be performed within 42 days preceding Dose 1.
b The Monitor Rating Form will be used by the same 2 therapists to provide ratings from Dose 1 up to 3 weeks postdose that focus on integration.
c Participants who do not complete both doses of TRP-8802 will return to the clinic within 28 days after their last dose of study intervention for an End of Therapy Visit.
d Participants should be supine and rested for at least 5 minutes before the ECG is recorded.
e A urine pregnancy test will be performed and results determined locally (Section 8.3.2).
f Urine drug and breath alcohol testing will be performed and results determined locally. Breathalyzer and COVID-19 test will be performed only on dosing days. (Section 8.3.3)
g A result of "severe depression" on PHQ-8 will exclude the participant from the study.
h Includes heart rate, systolic and diastolic blood pressure preferably with an automated device. Participants should be supine and rested for at least 5 minutes in a quiet setting before testing.
i PI-NRS pain diary is to be completed daily, by the participant and checked for completeness by study site staff at each on-site visit indicated (Section 8.2.1.1).
j All AEs and SAEs are to be recorded at the times indicated regardless off attribution.
k Medical occurrences that begin before Baseline but after obtaining informed consent will be recorded as medical history, not as AEs.
l Wear wrist actigraph Day 1 to 14 and Day 50 to 64
m To be performed prior to and approximately 7 hours after dosing
n To be performed approximately 7 hours after dosing.
o Qualitative written assessment is to be completed at Visit 14 only.

2. Introduction

Psilocybin 3-[2-(dimethylamino) ethyl]-1H-indol-4-yl] dihydrogen phosphate is a natural product produced by numerous species of Psilocybe mushrooms. The phosphate group is enzymatically cleaved in the body to produce psilocin, an agonist at a variety of serotonin receptors, the most important of which, for its behavioral effects, is the 5-hydroxytryptamine $(5\text{-HT})_{2A}$ receptor (Carhart-Harris 2014; Nichols 2004). Psilocybin was first isolated from Psilocybe mushrooms in 1957, followed by de novo synthesis in 1958 (Passie 2002). It was marketed worldwide in the 1960s as Indocybin™ for experimental and psychotherapeutic purposes. Although it was well tolerated and demonstrated potentially useful effects, it was classified as a controlled substances in the United States and designated as a Schedule I Controlled Substance in 1970; thus, it was effectively removed from clinical use or scientific study.

Psilocybin and similar drugs, such as lysergic acid diethylamide and mescaline, fall into a pharmacological class that are referred to in this application as "classic psychedelics" to differentiate them from other psychoactive substances (3,4 methylenedioxy—methamphetamine [MDMA]) that have different psychological/behavioral effects and different adverse effect profiles and risk/benefit ratios than psilocybin (Carhart-Harris 2013; Nutt 2010). Several lines of evidence suggest that serotonergic hallucinogens, such as psilocybin, have clinical potential for inducing therapeutically beneficial behavior change in patients with a variety of psychiatric conditions (Carhart-Harris 2013). TRP-8802 is being developed for the treatment of FM, other forms of nociplastic pain and overeating disorders.

The pharmacokinetics (PK), pharmacology, and human metabolism of psilocybin are well known and well characterized. Psilocybin has been used as a single agent and as an adjunctive treatment in adult populations. Psilocybin is administered orally and has been studied in open-label and double-blind, controlled trials. Dosing regimens have ranged from 0.014 mg/kg to 0.6 mg/kg, administered as either a single dose or multiple doses weeks apart (Tryp-8802 Investigator's Brochure [IB]).

Thousands of participants have received psilocybin under controlled conditions in a clinical setting for various indications, with subsequent results published in peer-reviewed journals (Rucker 2017; Metzner 2005). These clinical trials have demonstrated an improvement in symptoms of anxiety, depression, substance use disorder, and other complex neuropsychological conditions. Previous studies in healthy participants have shown oral psilocybin to be well tolerated. No drug- related serious adverse events (SAEs) were reported. Common AEs that were observed after psilocybin administration included cardiovascular (increased blood pressure [BP] and heart rate [HR]), gastrointestinal (nausea, vomiting, and diarrhea), and headache. As these studies were predominantly performed in an academic setting, safety reporting criteria and the level of data verification varied greatly between studies, but these data can be used to elucidate the expected adverse event profile of TRP-8802.

Fibromyalgia is a chronic syndrome of widespread musculoskeletal pain that often manifests with a cluster of co-occurring symptoms, including sleep disturbances, fatigue, cognitive

dysfunction, and mood problems including anxiety and depression. TRP-8802 therapy delivered in concert with psychotherapy may be a safe and effective treatment for symptoms associated with FM. The pressing need for effective FM treatments, the known safety of psilocybin therapy, and the mechanistic plausibility for potential benefit provide a rationale for investigating TRP-8802 therapy as a treatment for FM.

This is an open-label pilot study to assess the clinical benefit of oral TRP-8802 in concert with psychotherapy to treat chronic pain symptoms in patients with FM. Participants will undergo an initial pain phenotyping assessment and will complete a daily electronic pain diary until the end of active intervention. TRP-8802-psychotherapy intervention, the structure of which has been used in previous psilocybin clinical trials, will begin. During the two study drug administration sessions, participants will receive TRP-8802 in a comfortable setting under the guidance of two therapists. Participants will have an in-person study visit the day after each TRP-8802 administration visit to ensure their safety and comfort. Psychotherapy with the same two therapists will occur between and after TRP-8802 sessions with a focus on integration, helping participants gain insight and understanding from the experience. After the final dosing session, participants will undergo 3 weekly integration sessions, and then complete a post-treatment deep phenotyping session. Participants will complete patient reported outcome questionnaires at 84 and 168 days after the final TRP-8802 dose to examine persistence of changes.

2.1. Study Rationale

Fibromyalgia is a chronic pain condition that affects 2% to 4% of the population and is characterized by widespread pain as well as a cluster of co-occurring symptoms that include sleep disturbances and cognitive fog. Current treatments for FM are inadequate and there is an unmet need for treatment. Fibromyalgia treatment is challenging: many nonpharmacological therapies are inaccessible due to cost and lack of treatment providers, and most pharmacological therapies are only modestly effective and cause a significant side-effect burden. Some researchers have proposed that psychedelic drugs, such as psilocybin may have potential therapeutic value for treating FM and chronic pain.

Much of this interest has been generated by the results from small clinical trials among individuals with psychiatric disorders such as anxiety, depression, and addiction (Carhart-Harris 2021; Davis 2021a; Carhart-Harris 2018; Johnson 2017; Carhart-Harris 2016; Griffiths 2016; Ross 2016; Johnson 2014; Grob 2011), which show remarkable improvements in otherwise seemingly intractable conditions. Studies with modern neuroimaging techniques (e.g., functional connectivity magnetic resonance imaging [fMRI]) have shown that psilocybin dramatically alters maladaptive patterns of connectivity between different brain regions, which in combination with psychotherapy may promote improved clinical symptoms. Basic science research has identified the serotonin 5-HT_{2A} receptor as the primary target for psychedelics – a finding of interest given that polymorphisms in the encoding 5-HT_{2A} gene are associated with FM and chronic widespread pain (Nicholl 2011; Bondy 1999). While case series and retrospective surveys do suggest that psychedelic use may improve chronic pain due to cluster headache/migraine (Schindler 2015), phantom limb pain (Ramachandran 2018), and nociplastic and neuropathic pain (Castellanos 2020), no studies have examined the potential role of psychedelics in FM.

To better understand the potential benefits of psychedelics in chronic pain management, we are conducting this pilot clinical study with TRP-8802 among individuals with FM. Key procedures have been adapted from other clinical trials using psilocybin (Davis 2020), including psychotherapy sessions for participants to both prepare for and to integrate the TRP-8802 experience after administration.

2.2. Background

Nonclinical in vivo and in vitro studies of psilocybin found via literature searches demonstrate that when administered orally to rats psilocybin is rapidly dephosphorylated to psilocin in the intestinal mucosa by alkaline phosphatase and a nonspecific esterase, with approximately 50% of the total volume of psilocin absorbed from the digestive tract (Kalberer 1962). Maximum plasma levels are achieved after approximately 90 minutes (Chen 2011). When administered systemically (i.e., bypassing the gut), initial psilocybin metabolism is performed by tissue phosphatases, with in vitro studies indicating the kidneys as being among the most active metabolic organs (Horita 1961). Across species tested, the highest levels of psilocin were found in the neocortex, hippocampus, and thalamus (Hopf 1974).

Recent clinical studies using pharmaceutical-grade oral psilocybin under controlled conditions have been performed in healthy volunteers and various subpopulations to characterize the safety profile and evaluate the biological response (Tryp-8802 IB). The clinical studies presented similar safety profiles, with both psychological and physical AEs reported. During dose sessions, the most common adverse psychological events included anxiety, negative emotional states and paranoid/delusional thinking, and the most common physical effects were increased BP and HR, mild nausea, and mild headache.

Preliminary efficacy of psilocybin in clinical studies showed an improvement in symptomatic response in indications including substance use disorder, treatment resistant depression, and anxiety. Overall, psilocybin has been well tolerated at the doses examined in the clinical studies.

A detailed description of the chemistry, pharmacology, efficacy, and safety of TRP-8802 is provided in the current Tryp-8802 IB.

2.3. Benefit/Risk Assessment

Information about the known and expected benefits and risks and reasonably expected adverse events of TRP-8802 may be found in the Tryp-8802 IB.

Due to the psychoactive nature of TRP-8802, it should only be administered in a controlled setting per this clinical protocol. The safety of participants in this study will be enhanced by testing within a “set and setting” protocol as described by Lyons (2018) and by Johnson (2008). By addressing the set (the emotional/cognitive/behavioral state/mindset and expectations of study participants before TRP-8802 exposure) and setting (the physical environment in which the exposure occurs) of the experience, the risk of participants reporting an event which is distressing or injuring themselves can be reduced. Participants will be asked to discuss their session experience thoroughly with the goal of maximizing its therapeutic benefit.

Hallucinogen-persisting perception disorder (HPPD) is a very rare but potentially serious disorder that may occur as a significant adverse effect with the use of psychedelic compounds (mainly lysergic acid diethylamide [LSD]). It is characterized by symptoms such as visual disturbances, derealization, and depersonalization that last from weeks to years after use (Espiard 2005). No cases of HPPD have been reported in volunteers given psilocybin in recent research studies (Griffiths 2016, Studerus 2012, Griffiths 2011). In studies involving cancer patients examining cancer-related anxiety and depression, no cases of HPPD were identified and no patients developed any symptoms of paranoia or anxiety that required pharmacological intervention or anything more than reassurance from session therapists (Studerus 2011).

The risk of experiencing HPPD with 2 doses of TRP-8802 is expected to be very low, and the risk of its occurrence will be reduced by screening participants for potential risk factors such as severe substance use disorder and by excluding people reporting HPPD or other significant adverse events after prior use of hallucinogens. As these symptoms can present even after the duration of the study, participants will be educated about HPPD. If the symptoms were to occur, participants will be instructed to inform the study team immediately (during the study period), and to seek medical care (after the study period), to rule out HPPD.

Higher doses of psilocybin (greater than 0.3 mg/kg) also may transiently lead to elevated mean BP, peaking 30 to 60 minutes following psilocybin administration and returning to baseline levels after 90 to 180 minutes without necessitating further interventions (Griffiths 2006; Hasler 2004). The severity of elevations in BP was usually asymptomatic and was graded as mild or moderate. Although several subjects in a University of Wisconsin dose-escalation study reached BP elevations that were graded as moderate, they remained asymptomatic (Brown 2017). It is not clear whether the changes in BP and HR are due to the elevated psilocin concentration directly or to the psychedelic effect caused by this active metabolite. Psilocybin appears to produce only slight sympathetic system activation (Hasler 2004; Gouzoulis-Mayfrank 1999).

Transient elevations of HR were common in subjects receiving psilocybin at doses of 0.3 mg/kg or more. The time course of these elevations in HR is similar to those seen for the elevation in BP, peaking between 60 to 120 minutes after the dose. This is similar to time of peak psilocin concentrations and peak psychedelic effect. Again, it is not clear whether or not the changes in BP and HR are directly due to the elevated psilocin concentration or caused indirectly by the psychedelic effect. In a phase 1 dose-escalation study in healthy volunteers, there were several instances in which mild bradycardia and tachycardia were noted. Psilocybin resulted in an increased HR, with slightly higher mean change from baseline in HR (ΔHR) at higher psilocybin doses and corresponding higher psilocin exposures (Dahmane 2021). The maximum mean ΔHR was observed at the time of psilocin maximum observed concentration (C_{max}) (i.e., at 2 hours post dose) in nearly all psilocybin dose groups, and mean ΔHR decreased with decreasing psilocin concentration at subsequent time points. Instances of bradycardia or tachycardia were unimodal, with no swing between bradycardia and tachycardia after a given dose. The episodes of bradycardia and tachycardia reported in recent studies were asymptomatic (“mild” or Grade 1) and did not require treatment (Tryp-8802 IB). Further information can be found in the current Tryp-8802 IB.

Mild headaches are common within the 24 hours after a dose of psilocybin. No auras or photo/phonophobia are associated with these headaches, which respond well to a single dose of

acetaminophen. The headaches did not appear to be dose-related in one study, with no higher incidence after doses of 0.6 mg/kg versus 0.3 mg/kg (Brown 2017).

Taking into account the measures taken to minimize risk to participants in this study, the known and potential risks identified in association with TRP-8802 are justified by the anticipated benefits that may be afforded to participants with FM.

3. Objectives and Endpoints

Table 3: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety of TRP-8802 under the conditions of this trial	Safety during dosing sessions: vital signs (HR, BP) (Section 8.1.1); AEs (Section 8.1.2), Safety during trial: AEs
Secondary	
To evaluate the clinical benefit of oral TRP-8802 in concert with psychotherapy to treat chronic pain symptoms in patients with FM	
To assess other potential therapeutic effects of TRP-8802 assisted therapy on FM symptoms	Participant self-reported outcomes: • pain interference (Section 8.2.1.2) • sleep (Section 8.2.1.3) • chronic pain acceptance (Section 8.2.1.4) • Patient Global Impression of Change (PGI-C) (Section 8.2.1.5)

Objectives	Endpoints
Exploratory	
To characterize other TRP-8802 clinical and PD effects	Patient reported outcomes relevant to chronic pain (Sections 8.2.2.1, 8.2.2.2) • FM survey score, affect, catastrophizing, fatigue, anxiety, depression, cognitive impairment Dosing-specific patient reported outcomes (Section 8.2.2.3) • Mystical experiences • Challenging experiences • Psychological insight Dosing-specific therapist reported outcomes • Monitor rating scale (Section 8.2.2.3) Qualitative written assessment (Section 8.2.2.4) to determine subjective participant experiences Self-pain enmeshment (Section 8.2.2.5) Self-complexity task (Section 8.2.2.6) QST (Section 8.2.3.1) • Change in cuff P40 pre- and post-intervention • Visual hypersensitivity fMRI (Section 8.2.3.2) • Change in insula-default mode network connectivity • Change in Glx and/or GABA in anterior insula • Change in evoked pressure pain (tonic cuff) • Change in grey matter volume Wrist actigraphy (Section 8.2.3.3) • Sleep onset latency • Wake after sleep onset • Total sleep time • Sleep efficiency (%)

AEs=adverse events; BP=blood pressure; FM=fibromyalgia; GABA=gamma aminobutyric acid; Glx=glutamine+glutamate; HR=heart rate; P40=pain rating of 40 out of 100; PD=pharmacodynamic; QST=Quantitative Sensory Testing.

Note: The aggregate weekly pain score is over a 7-day period.

4. Study Design

This is a single-arm, single center, open-label (uncontrolled) pilot study in participants with FM.

4.1. Overall Design

- All participants must have FM or have had FM symptoms for at least a year, and meet the 2016 FM Survey Criteria for FM. Exclusion criteria include certain co-morbid psychiatric disorders (e.g., psychotic disorders, bipolar I or II disorder, substance use disorder), history of a medically significant suicide attempt, and use of certain medications (e.g., anti-depressants).
- All participants enrolled in the study are expected to receive 2 doses of TRP-8802 separated by 2 weeks during in-center study intervention sessions.
- "Active intervention" includes baseline deep phenotyping, preparation, study drug administration, integration, and EOT deep phenotyping.
- Study visits may have visit "windows" as shown in the Schedule of Activities (SoA, Section 1.3)
- Further details regarding dosing and therapy sessions are provided in the Psychotherapy Manual.
- One of the physicians associated with the study will have a brief visit with the study participant during screening or prior to the first dosing session.
- The Lead Facilitator will be a doctoral level PhD/MD-level psychotherapist (or equivalent). Acceptable degrees for Lead Facilitators are: Clinical and Counseling Psychologists (PhD/PsyD), Physicians and Psychiatrists (MD or DO) or Masters of Social Work (MSW). The Co-Facilitator will have at least a bachelor's degree in mental health and at least one year of clinical experience in a licensed mental health care setting.
- The total duration of study participation for an individual participant is approximately 8 months, including screening, preparation, administration, integration, EOT, and follow-up.
- The total planned duration of the entire study is expected to be 18 months.
- There are no provisions for extending the study for any participants or for entry to roll-over studies.
- An SRC will be responsible for the assessment of safety and to make recommendations with regard to study progression (Appendix 1, Section 10.1.5).

The timing and a description of these assessments are also provided in the SoA, Section 1.3 and in Section 8.

4.1.1. Screening Period (Visit 1, Day -42 to Trial Initiation)

Once candidates are pre-screened for interest and eligibility, they will complete a screening visit in which the informed consent process (Appendix 1, Section 10.1.3) is completed before any other procedures are assessed. When inclusion and exclusion criteria are confirmed, other assessments are completed as follows:

- demographic and baseline characteristics
- medical history
- prior/concomitant medications

- Structured Clinical Interview for Diagnostic and Statistical Manual for Mental Disorders 5th Edition (SCID-5) and SCID-5 for Personality Disorders (SCID-5-PD)
- The Life Events Checklist for DSM-5 (LEC-5) (Weathers 2013) will be used to assess past history of or exposure to trauma. Participants indicate how many of 16 potentially traumatic events (e.g., natural disaster, physical assault) they experienced personally or witnessed, as well as an additional item assessing any other very stressful event or experience. The number of events that participants indicate happened to them personally is summed, with scores potentially ranging from 0 to 17. Participants will be asked these questions verbally (recorded by study staff) or to fill out the questionnaire themselves.
- 12-lead electrocardiogram (ECG)
- pregnancy test for women of childbearing potential (WOCBP)
- urine drug tests
- vital signs
- patient reported outcomes (Patient Health Questionnaire depression scale-8 [PHQ-8], Columbia Suicide Severity Rating Scale [C-SSRS], 2016 FM Survey Criteria)
- Comprehensive Metabolic Panel (CMP): Na+, K+, Cl-, HCO3-, Ca++, Mg++, P, BUN, creatinine, glucose, total bilirubin, albumin, ALT, AST, GGT, CK, LDH, alkaline phosphatase
- Hematology: CBC with white cell differential and platelet count

Any clinically significant abnormal laboratory findings for blood chemistry or hematology would be exclusionary from study participation.

4.1.2. Baseline (Visit 2, Day 1)

Assessments on Day 1 will be considered baseline assessments. On Day 1, participants will undergo a rigorous pain phenotyping assessment (i.e., deep phenotyping) as shown in the SoA (Section 1.3). A validated battery of patient reported outcomes includes the following:

- STOP-Bang (Chung 2016; Nagappa 2015) will be used to screen for sleep apnea which can interfere with sleep. The STOP-Bang questionnaire consists of 8 questions that assess risk of sleep apnea, including snoring, tiredness, whether anyone has observed the person stop breathing in their sleep, high BP, body mass index, age, neck circumference > 16 inches, and sex.

From this deep phenotyping session until the end of active intervention (28 days after final TRP-8802 dosing session), participants will complete a daily electronic pain diary to evaluate pain level on a scale of 0 to10, on the Pain Intensity-Numeric Rating Scale (PI-NRS).

4.1.3. Preparation Period (Visits 3 and 4, Day 11 and Day 18)

Participants will begin psychotherapy intervention, the structure of which has been used in previous psilocybin clinical trials. As with other psilocybin studies, discussions will include information on the participant's life history, current situation in life, as well as the participant's understanding, expectations, and intentions for the TRP-8802 administration sessions. In brief, during the approximately 8 hours of preparatory therapy at Visits 3 and 4, participants will develop rapport with two assigned therapists, learn about FM, as well as build comfort and

understanding around the physical space and what will occur in the dosing sessions. Details of these sessions are provided in the Psychotherapy Manual. One of these preparatory therapy sessions may occur via a HIPAA-compliant video conferencing platform if necessary.

4.1.4. TRP-8802 Administration Period (Visit 5 to Visit 9, Day 22 to Day 37)

The procedures used during the administration period will be consistent with those from other published studies using psilocybin assisted therapy (Davis 2021a). Participants will be asked to eat a low-fat breakfast before reporting to the Rachel Upjohn Building for their dosing sessions. Before administration of study drug, participants will provide urine samples that will be tested for drugs (Section 8.3.3) as well as for pregnancy for WOCBP (Section 8.3.2); tested for COVID-19; and a breath alcohol test will also be administered (Section 8.3.3). All tests must be negative for participants to proceed. Participants will also complete pre-session questionnaires and a brief interview with study personnel. The purpose of this brief interview is to assess if the session is contraindicated. If so, then that session will be postponed if possible.

Participants will receive an initial 15 mg dose of TRP-8802 (lower dose) on Day 22 followed by the second dose of 25 mg (higher dose) on Day 36. TRP-8802 will be administered in a comfortable setting under the guidance of the same two therapists from the preparation period. The 15 mg dose can be repeated at Dose 2 if the participant or Investigator determines that the higher dose is not advantageous and/or may not provide further benefit, based on observations for Dose 1. Participants will have an in-person study visit the day after each dose administration (Day 23 and Day 37) to ensure participant safety and comfort. There will also be a visit (virtual using a HIPAA-compliant video conferencing platform or in-person) 7 days after administration of the first dose (Day 29) to integrate the first experience and prepare the second dosing day.

During the dosing sessions, which will take at least 8 hours, two therapists will be present in the room and available to support participants' physical and emotional needs. A study physician will be on call and within 5 minutes of the session room during the first 3 hours or until the peak effects of psilocybin have abated, and will remain available for the remainder of the course of the TRP-8802 dosing session if needed for consultation. During these sessions, participants will be instructed to lie on a comfortable couch or bed, wear eyeshades, and listen to music through headphones, all of which are meant to enhance and encourage internal attention and reflection. Participants will be encouraged by the therapist to direct their attention inward. Recumbent BP and HR will be monitored (Section 8.1.1) until the drug effects have lessened. There will be an automated external defibrillator located on site and a crash cart containing medicine (Section 6.8.1) and equipment for emergency resuscitation.

During the same period as the vital signs measurements, therapists will also complete the monitor rating form, which includes questions about the presence/intensity of behaviors, signs, and reported symptoms, such as peacefulness, yawning, nausea/vomiting, quantity of speech, anxiety, sleepiness, crying, restlessness, visual changes, euphoria, and feelings of unreality. These sessions will be video and audio recorded. After the study drug effects have subsided, participants will complete questionnaires that assess the subjective experiences of the TRP-8802 dosing session, and the therapists will complete questionnaires that assess participant mood and safety. Participants will be asked to process the experience at home by writing a reflection about

their experiences during the dosing session (Section 8.2.2.4). This reflection will be discussed at follow-up meetings.

4.1.5. Integration Period (Visits 10 to 12, Day 43 to Day 57)

After the final dosing session, participants will have 3 weeks of therapy integration sessions (up to 2 hours/week). Psychotherapy will occur during this period with a focus on integration, helping participants gain insight and understanding from the experience. These visits can occur in person or via a Health Insurance Portability and Accountability Act (HIPAA)-compliant video conference platform. Sleep (wrist actigraphy) will also be assessed.

4.1.6. End of Therapy (Visit 13, Day 64)

The EOT assessment will occur approximately 28 days after the last dosing session, when participants will complete their final deep phenotyping session. Regardless of whether or not a participant completes both dosing sessions or chooses to discontinue the study early, participants will be asked to complete all EOT and follow-up assessments if they have received at least 1 dose of TRP-8802.

4.1.7. Follow-up Period (Visits 14 and 15, Day 120 and Day 204)

Patient reported outcome measures will be administered to each participant at 84 and 168 days after the final dose to examine persistence of changes of TRP-8802 and the therapy sessions.

4.2. Scientific Rationale for Study Design

This is a pilot study designed to understand the safety and potential benefits of TRP-8802 in concert with psychotherapy in the chronic pain management of FM. Participants must be 25 to 64 years of age, inclusive, at the time of signing the informed consent form. This age range is included as the prevalence of FM increases with age and treatment outcomes remain poor (Sarzi-Puttini 2020).

4.3. Justification for Doses

A single-site, open-label, dose-escalating clinical trial was conducted to evaluate the PK, safety, and cardiovascular effects of an oral formulation of psilocybin in 12 normal, healthy adults (Brown 2017). Psilocybin was administered in sequential, escalating oral doses of 0.3, 0.45, and 0.6 mg/kg. with a mean dose level, as defined by the average participant weight, of 23.4 mg (0.3 mg/kg), 35.1 mg (0.45 mg/kg), and 46.9 mg oral psilocybin (0.6 mg/kg). The dose range used in the study by Brown (2017) covers the dose range proposed herein, which uses fixed doses of 15 mg and 25 mg. Several other studies of psilocybin administered in this dose range are presented in the Tryp-8802 IB.

No parent psilocybin was found in plasma or urine after a single dose of psilocybin, confirming the rapid metabolism of psilocybin to psilocin (Dinis-Oliveira 2017). The PK profile of psilocin was linear within the 2-fold range of doses, and the elimination half-life of psilocin was 3 hours (SD 1.1). In general, all 3 dose strengths were physically and psychologically well tolerated, and no serious physical or psychological AEs up to 30 days after dose administration were reported.

This 2-dose level design has been used in several studies, including the recent investigation of psilocybin in major depressive disorder (Davis 2021a). The first TRP-8802 dosing session (15 mg) is not expected to produce full psychedelic effect, but is instead meant to help familiarize participants with study intervention effects and study procedures. The second, higher-dose TRP-8802 dosing session (25 mg) is expected to produce a greater likelihood of therapeutic effect. The 2-dose level design also allows the investigators to assess the suitability of the participant to the study procedures and to gauge whether the participant is suitable for receiving the higher dose at Dose 2. Additionally, the 2-dose level design is being used to reduce the likelihood of an unexpected AE in participants who may have higher bioavailability and/or higher rates of conversion to psilocin.

4.4. End of Study Definition

A participant is considered a study completer if they complete all phases of the study through Visit 13 (EOT). Participants will be encouraged to complete follow up assessments (Visits 14 and 15) which occur 3 and 6 months after the final dose. Study participation ends after Visit 15 (final study visit). A participant who discontinues the study early/withdraws from the study will be asked to complete the EOT and both follow-up visits.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. Study Population

Candidates who express an interest in participating in this study will undergo pre-screening. Prior to coming in for the screening visit, potential participants will be asked questions to see if they meet the inclusion/exclusion criteria. If they meet these criteria and are interested in participating, potential participants will provide informed consent electronically or will be invited to come in for the official screening visit, at which time obtaining informed consent will be completed.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, will not be permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 25 to 64 years of age, inclusive, at the time of signing the informed consent form.

Type of Participant and Disease Characteristics

2. Participant has had a diagnosis of FM for ≥ 3 months or has had FM symptoms for at least 1 year per self-report.
3. Participant must meet criteria for FM per the 2016 FM survey criteria.
4. Concurrent psychotherapy is allowed if the type and frequency of the therapy has been stable for at least 2 months prior to screening and is expected to remain stable during participation in the study.
5. Participant must be a non-smoker (tobacco) per self-report.
6. Participant must be medically stable as determined by screening for medical problems via a personal interview and/or, a medical questionnaire, and an ECG, within 1 month of starting active intervention (performed during screening).
7. Participant must agree to consume approximately the same amount of caffeine-containing beverage (e.g., coffee, tea, cola) that he/she consumes on a usual morning, before arriving at the research unit on the mornings of TRP-8802 session days. If the participant does not routinely consume caffeinated beverages, he/she must agree to not do so on TRP-8802 session days.
8. Participant must agree to refrain from using any psychoactive drugs, including alcoholic beverages and nicotine, within 24 hours before and after each TRP-8802 administration. The exception is caffeine.
9. Participant must agree to not take sildenafil (Viagra®), tadalafil, or similar medications within 72 hours before and after each TRP-8802 administration.

10. Participant must agree to not take any pro re nata (PRN) medications on the mornings of TRP-8802 sessions.
11. Participant must have at least a high school level of education or equivalent (e.g., General Educational Development [GED] Test).
12. Up-to-date vaccination for COVID-19 (at least two doses).

Sex and Contraceptive/Barrier Requirements

13. Contraceptive use by women and men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Adequate birth control methods include intrauterine device, injected/implanted/intravaginal/transdermal hormonal method, oral hormones plus a barrier contraception, abstinence, vasectomized sole partner, or double barrier contraception.

    a. Females of reproductive potential must agree to use effective birth control for the duration of active intervention (defined as the time from the Baseline [deep phenotyping] visit until the EOT [deep phenotyping] visit).

    b. Sexually active male participants and/or their female partners must agree to use effective birth control for the duration of active intervention (defined as the time from the Baseline [deep phenotyping] visit until the EOT [deep phenotyping] visit) of the male participant. Male participants must also agree not to donate sperm for the duration of active intervention.

Informed Consent

14. Participant has provided informed consent as described in Appendix 1, Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Participant has had (within the past 1 year) a cardiovascular condition such as coronary artery disease, stroke, angina, uncontrolled hypertension, a clinically significant ECG abnormality (e.g., atrial fibrillation), prolonged QTc interval (i.e., QTc > 450 msec), artificial heart valve, or transient ischemic attack.
2. Participant has epilepsy with a history of seizures.
3. Participant has insulin-dependent diabetes.

4. Participant is taking an oral hypoglycemic agent and has a history of hypoglycemia.
5. Participant has active auto-immune disease (e.g., lupus, rheumatoid arthritis).
6. Participants has any clinically significant lab abnormalities per a complete blood count and metabolic panel (e.g., elevated liver enzymes). Please see screening in section 4.1.1.
7. Participant has a current or past history of meeting Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria for schizophrenia spectrum or other psychotic disorders (except substance/medication-induced or due to another medical condition), or bipolar I or II disorder measured via SCID-5 and SCID-5-PD.
8. Participant has a current or past history (within 1 year) of meeting DSM-5 criteria for a moderate or severe alcohol, tobacco, or other drug use disorder (excluding caffeine) measured via relevant questions from the SCID-5.
9. Participant has a history of a medically significant suicide attempt.

Prior/Concomitant Therapy

10. Participant is taking psychoactive prescription medication (e.g., opioids, tramadol, benzodiazepines) on a regular basis (i.e., more than 2 times a week).
11. Participant is currently taking 300mg/day of bupropion or antidepressants other than selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs).
12. Participant is currently taking monoamine oxidase inhibitors (MAOIs) on a regular basis (daily or most days). For individuals who have intermittent or PRN use of such medications, TRP-8802 sessions will not be conducted until at least 5 half-lives of the agent have elapsed after the last dose.
13. Subjects taking prohibited medications. The list of prohibited medications should include antihypertensive medications, UGT1A9 or 1A10 inhibitors (e.g., regorafenib, rifampicin, phenytoin, eltrombopag, mefenamic acid, diflunisal, niflumic acid, sorafenib, isavuconazole, deferasiroxor, ginseng) and aldehyde or alcohol dehydrogenase inhibitor (e.g,, disulfiram).
14. Participant is currently taking prohibited drugs of abuse, including methamphetamine, illicit opioids (e.g., heroin), cocaine, 3,4-Methylenedioxymethamphetamine (Ecstasy/Molly), or hallucinogens (e.g., mescaline or peyote).
15. Participant has any use of hallucinogens in the past 6 months or has had a total lifetime hallucinogen use of 10 or more times.
16. Participant tests positive for cocaine, methamphetamine, or opioids on urine drug testing.

17. Participant has a psychiatric condition judged to be incompatible with establishment of rapport or safe exposure to TRP-8802.

Prior/Concurrent Clinical Study Experience

18. Participant is currently in another clinical trial.

Diagnostic assessments

19. Participant has a significant suicide risk as defined by:
    a. suicidal ideation as endorsed on items 4 or 5 on the C-SSRS within the past year at Screening or at Baseline; or
    b. suicidal behaviors within the past year; or
    c. clinical assessment of significant suicidal risk during participant interviews
20. Participant has severe depression as measured through PHQ-8 at Screening.

Other Exclusions

21. Participant is pregnant (as indicated by a positive urine pregnancy test assessed at Screening and before each TRP-8802 session) or nursing.
22. Participant is a WOCBP and sexually active, or a man and sexually active, and not practicing an effective means of birth control.
23. Participant has a confirmed first- or second-degree relative with schizophrenia spectrum or other psychotic disorders (except substance/medication-induced or due to another medical condition), or bipolar I or II disorder.

5.3. Lifestyle Considerations

Some lifestyle considerations (e.g., diet, smoking habits, alcohol, or recreational drug consumption) could be of relevance for this study. Therefore, the following restrictions apply:

- Caffeine-containing beverages are allowed during the study, including on TRP-8802 session days. However, participants are expected to consume approximately the same amount of caffeine-containing beverages that they usually consume before arriving at the research unit on the mornings of TRP-8802 drug sessions.
- Participants must be non-smokers (tobacco) before and during the entire study.
- Psychoactive drugs, including prescription and recreational drugs, are only allowed during the study period as described in the study protocol.
- Alcoholic beverages and psychoactive drugs are not allowed within 24 hours before and after each TRP-8802 administration.
- For 7 days before each TRP-8802 session, participants must refrain from taking any nonprescription medication, nutritional supplement, or herbal supplement except when approved by the Principal Investigator. Exceptions must be evaluated by the Principal

Investigator and may include acetaminophen, non-steroidal anti-inflammatory drugs, and common doses of vitamins and minerals. No PRN medications are allowed on the mornings of TRP-8802 administration.
- Drugs such as sildenafil (Viagra®), tadalafil, or similar medications are not allowed within 72 hours before and after each TRP-8802 administration.

There are no restrictions on physical activity during the study. TRP-8802 session days will be held under the supervision of two therapists who are present throughout the session. Sessions will be conducted in a room designed to be quiet, comfortable, and aesthetically pleasing, and participants are encouraged to wear eyeshades and listen to a program of music through headphones during the drug exposure to aid them in focusing their attention inward.

Participants should agree to not drive or operate machinery on the day of TRP-8802 administration. Participants must agree to be driven home after TRP-8802 drug sessions. Once they are considered to be medically stable post-dose by the Investigator, participants will be discharged and should accompanied for the evening by a family member or caregiver.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. If a participant is taking an exclusionary medication at screening, and the participant and their health care provider(s) agree that it is appropriate to change medication(s), then rescreening may occur after the appropriate washout period.

Rescreened participants should be assigned a new participant number for every screening/ rescreening event.

5.5. Criteria for Temporarily Delaying Enrollment or Administration of Study Intervention

If any of the stopping rules below is met, dosing will pause until the SRC convenes (either routine or ad hoc) to review details of the event and/or additional data. If, after further review of the data, the SRC determines that no stopping rule has been met (e.g., AE determined to be unrelated to the study drug) or that if a stopping rule has been met there is a way to safely continue the trial (e.g., appropriate safety monitoring can be implemented), then dosing may resume. The occurrence of any of the following events will result in a temporary halt of dosing:
- one SAE considered at least possibly related to the study drug
- one Grade 3 or Grade 4 AE considered at least possibly related to the study drug
- clinically similar Grade 2 AEs considered at least possibly related to the study drug in 2 participants

The study may be discontinued at any time by the Institutional Review Board (IRB), the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

6. Study Intervention(s) and Concomitant Therapy

In this protocol, study intervention is the combination of the investigational TRP-8802 and psychotherapy. This Section covers the administration of TRP-8802; psychotherapy treatment is covered in more detail in the Psychotherapy Manual.

6.1. Study Intervention TRP-8802

TRP-8802 intervention, doses, and route of administration are presented in Table 4.

Table 4: Study Treatments Administered

Intervention Name	TRP-8802
Type	Drug
Dose Formulation	Capsule
Unit Dose Strengths	5 mg and 25 mg
Dosage Levels	15 mg (3 x 5 mg) and 25 mg (1 x 25 mg)
Route of Administration	Oral
Use	Experimental
Sourcing	Provided centrally by the Sponsor
Packaging and Labeling	TRP-8802 will be provided in high-density polyethylene bottles. Each bottle will be labeled in accordance with appropriate regulatory requirements.
Current/Former Name	Psilocybin
Manufacturer	Usona Institute

6.1.1. TRP-8802 Administration

Participants will be instructed to consume a light, low-fat breakfast before TRP-8802 administration. Capsules of TRP-8802 will be administered orally with 8 ounces of water at the research unit under the supervision of study staff. Capsules should not be opened or chewed. The drug session will be rescheduled if a friend or family member of the participant is not available to accompany them home after being discharged from the research unit.

6.1.2. Leaving the Research Unit

Participants will not be allowed to leave the research until the study staff makes the judgment that the effects of the study intervention have completely subsided. Participants will expected to be on the research site for at least 8 hours. The discharge criteria are as follows (all of the following must be met):

- A responsible friend/family member is available to accompany the participant home.

- The participant's clinical status is not deemed to be of concern by the clinical judgment of a study physician.
- The participant is deemed by study staff to be free of any acute drug effects.
- The participant believes they have approximately returned to their psychological baseline.
- The study staff judges that it is safe to discharge the participant.
- The participant expresses a readiness to go home.

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions of 15°C to 25°C have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- The investigator or designee must confirm appropriate temperature conditions of 15°C to 25°C have been maintained at the study site for all study intervention and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance including information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias

Efforts will be made to ensure a representative sample of the local FM community participates in the study. The chance of observer bias is minimized by the use of widely used, validated objective measures during the study. However, as this is an open-label pilot study, sources of bias will remain.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site staff will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Dose Modification

The only dose modification allowed would be with the second dose (of 2 planned doses) to be 15 mg (instead of 25 mg) if the participant or Investigator determines that the higher dose is not advantageous and may not provide further benefit.

The reason for dose modification must be noted in the source documents and case report form (CRF).

Note: If participants exhibit an increased risk of harm to self or others, or any other sign that continuing in the study would present undue risks the second dose should not be administered. Similarly, participants will not be allowed to continue with a second dose if they have adverse events such as psychosis or hypertension.

6.6. Continued Access to Study Intervention after the End of the Study

There are no provisions for any participant for extending the study or for entry to roll-over studies. There is no intervention planned after the end of the study.

6.7. Treatment of Overdose

For this study, any dose of TRP-8802 greater than the intended dose (15 mg [Day 22] or 25 mg [Day 36]) in a 24-hour time period will be considered an overdose.

No confirmed incidences of an overdose of pharmaceutical psilocybin have been reported. Previous clinical trials involved single or multiple doses of oral psilocybin in predefined quantities administered in a controlled environment. Should an accidental overdose occur, appropriate symptomatic measures should be initiated, followed by monitoring any AEs to resolution.

In the event of an overdose, the site staff should immediately contact the site physician, who will determine whether the participant should be treated with rescue medication and if further treatment is needed (e.g., emergency department visit). The participant should be closely monitored for any AE/SAE for at least 1 day. The quantity of the excess dose(s) should be documented in the source documents and the Study Drug Administration CRF.

6.8. Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant receives beginning at the time of screening or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days before each study drug session day, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

6.8.1. Rescue Medicine

The session therapists are trained to reassure the participants if they experience acute anxiety, agitation, paranoia, or panic. However, in the unlikely event that those symptoms do not respond to reassurance, or if a participant experiences a severe AE outside of the expected challenging experiences associated with psilocybin therapy, one of the session therapists will contact the on-call study physician. The study physician will use their clinical judgment to determine the most appropriate medical intervention.

The study site will supply rescue medication that will be obtained locally. The following rescue medications may be used:

- In the event of a psychiatric emergency, an oral benzodiazepine (e.g., lorazepam) will be available for on-site treatment of panic or anxiety. An oral antipsychotic (e.g., risperidone) will be available for on-site treatment of psychosis or severe agitation.
- In the event of symptomatic hypertension, labetalol or similar will be available for on-site treatment of symptomatic hypertension.
- In the event of new-onset chest pain, the participant will be evaluated in-person by the study physician to determine whether the pain is cardiovascular, musculoskeletal, or reflects acute panic/anxiety. Vital signs and ECG will be monitored (and compared to baseline measurements) for evidence of acute ischemia. Based on physician judgment, sublingual nitroglycerin (available on-site) may be administered as the standard of care for cardiac chest pain while Emergency Medical Services is called to transport the participant to an emergency department. The goal will be to transport an acutely decompensating patient to an emergency department prior to the point where advanced cardiac life support care is required.
- In the event of headache, ibuprofen (400 mg orally) or similar will be available for on-site treatment. If the study physician decides that the use of a rescue medication is warranted, then the study physician or a member of the nursing staff will administer the medication to the participant.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the CRF. In the unlikely event that a medical or psychiatric emergency occurs during a drug session and cannot be safely managed by study personnel using reassurance or medication, study staff will contact 911 so that the participant can be transported to an emergency medical department.

In the event that rescue medication is needed, the Investigator and study physicians may use their clinical judgment to implement a future dose modification (Section 6.5) or to discontinue future study intervention (Section 7.1) for that participant.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention before both doses of TRP-8802 are administered. If study intervention is permanently discontinued, the participant will not remain in the study, although they will be asked to complete study assessments. See the SoA (Section 1.3) for data to be collected at the EOT and follow-up visits.

If participants exhibit an increased risk of harm to self or others, or any other sign that continuing in the study would present undue risks the second dose should not be administered. Similarly, participants will not be allowed to continue with a second dose if they have serious adverse events such as psychosis or hypertension. Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study (Section 8.4.5).

7.1.1. Temporary Discontinuation

Temporary discontinuation of study intervention will not be allowed. A participant who discontinues study intervention will be considered to be discontinued from the study.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, the EOT and follow-up visits should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's research record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of a specific site or of the study as a whole is presented in Appendix 1 (Section 10.1.9).

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Audio and video recordings will be made for the length of the dosing session days. The recordings will be used for quality assurance and staff training purposes; they will not be used for any other purpose for this study.

8.1. Safety Assessments (Primary Endpoints)

Planned time points for all safety assessments are provided in the SoA (Section 1.3). Safety assessments will always be performed before efficacy assessments at each visit.

8.1.1. Vital Signs

Heart rate and BP will be assessed before TRP-8802 capsule administration and at 30, 60, 90, 120, 180, 240, 300, and 360 minutes after capsule administration. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones). Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. If a patient's blood pressure is >200 systolic or >110 diastolic for more than 15 minutes (i.e. 4 consecutive readings) they will be transferred to ED whether or not they are symptomatic.

8.1.2. Adverse events

Adverse events will be assessed throughout the study as detailed in Section 8.4.

New onset of suicidal ideation will be considered an AE. Suicidal ideation will be assessed during every in-person visit using the C-SSRS and clinical assessment during participant interviews. The C-SSRS was developed by researchers at Columbia University and is widely used in clinical and research settings (https://cssrs.columbia.edu/). Significant suicidal ideation is endorsed on items 4 or 5 on the C-SSRS.

8.2. Efficacy Assessments (Secondary and Exploratory Endpoints)

Planned time points for the efficacy assessments are provided in the SoA (Section 1.3).

All efficacy assessments measured by questionnaires or surveys will be collected electronically for inclusion in the electronic data capture (EDC) database.

8.2.1. Patient Reported Outcomes (Secondary Efficacy Endpoints)

8.2.1.1. Aggregate Worst Pain Score Change

To evaluate the efficacy of oral TRP-8802 to treat chronic pain symptoms in patients with FM, the aggregate worst pain intensity (0 to 10) on the PI-NRS at baseline (Days 1 to 7) will be compared to the 7 day (Days 57 to 63) aggregate immediately prior to the EOT visit (Day 64).

Pain will be measured daily using an electronic pain diary. Participants will receive a message via text or email at 6pm each evening with the PI-NRS questions. If the participant does not respond within 2 hours, a reminder text or email will be sent at 8pm. Response options will be closed at midnight. Participants who miss a day will be contacted the following day to remind them to complete their daily diary.

8.2.1.2. Pain Interference

Pain interference is the degree to which pain affects important aspects of an individual's life, such as social, cognitive, and physical activities. Pain interference will be assessed using the 4-item PROMIS pain interference scale from the PROMIS-29+2 Profile v2.1 (PROPr) which is published at HealthMeasures.net (2021).

8.2.1.3. Sleep

Sleep disturbance includes assessment of sleep quality, perceived ability to fall and stay asleep, satisfaction of sleep, and depth of sleep. Sleep disturbance will be measured using the PROMIS Sleep Disturbance Short Form 8b which is published at HealthMeasures.net (2021).

8.2.1.4. Chronic Pain Acceptance

The CPAQ-8 (Fish 2010) is a validated measure that assesses activity engagement and pain willingness (e.g., recognizing that trying to avoid or control pain may be maladaptive for chronic pain). Participants rate items on a 0 to 6 scale, with 0 being "never true" and 6 being "always true".

8.2.1.5. Patient Global Impression of Change

The PGI-C is a questionnaire that gauges the participant's response to medical interventions using a 7-point Likert scale ranging from 1 to 7 with 1 being "very much improved" and 7 being "very much worse" and has been used in many pain clinical trials (Dworkin 2008; Dworkin 2005).

8.2.2. Patient Reported Outcomes (Exploratory Endpoints)

8.2.2.1. Pain Mechanism Characteristics

The 2016 FM survey, a combined measure of widespread pain (using the Michigan Body Map [Brummett 2016] with number of painful sites 0 to19) and symptom severity (e.g., fatigue,

subjective cognitive problems, headache, poor mood, scores range 0 to 12 [Neville 2018; Brummett 2015; Janda 2015; Brummett 2013]), will be used to form a continuous proxy index of nociplastic pain characteristics (range 0 to 31) (Wolfe 2016; Wolfe 2011; Wolfe 2009).

8.2.2.2. Domains Relevant to Chronic Pain

Questionnaires that measure physical and mental traits associated with pain centralization will include:

- The catastrophizing scale from the Coping Strategies Questionnaires Pain (Rosenstiel 1983) assesses pain catastrophizing, a thinking style that has been associated with the progression of acute pain to chronic states and with generally poorer outcomes (Kratz 2015).
- The PROMIS-29+2 Profile v2.1 (PROPr) (Healthmeasures.net [2021]) will be used to assess multiple domains: physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles, pain interference, cognitive function, and pain intensity. The addition of the 2 cognitive functioning items differentiates this instrument from its parent the PROMIS Profile 29 (Hays 2018). The PROMIS-29+2 can also be used to calculate a preference score (PROMIS Preference, PROPr) (DeWitt 2020; DeWitt 2018; Hanmer 2018) Preference-based scores provide an overall summary of health-related quality of life on a common metric. Preference-based scores summarize multiple domains on a metric ranging from 0 (as bad as dead) to 1 (perfect or ideal health). Scores can be used in comparisons across groups and for cost-utility analyses. T-scores from the measure can be used to calculate a preference-based score. The PROMIS-29+PROPr is published along with all other PROMIS measures at HealthMeasures.net (2021). An optional addition to the PROPr is the use of items from the Patient Acceptable Symptom State Questionnaire. These items added to each domain allow for assessment of whether the patient believes each domain is adequately managed (Salaffi 2015)

8.2.2.3. Questionnaires and Forms Utilized During Dosing Sessions

- The Mystical Experience Questionnaire (MEQ30) has been widely used to assess the mystical experiences occasioned by psychedelics (Barrett 2015; MacLean 2011). This 30-item scale includes questions that assess mystical experiences, positive mood, transcendence of time and space, and ineffability.
- The Challenging Experience Questionnaire (CEQ27) assesses challenging experiences and has been frequently used in studies with psychedelics, including psilocybin. Questions assess the difficulty, meaningfulness, spiritual significance, and change in well-being attributed to the psychedelic experience (Barrett 2016).
- The Psychological Insight Questionnaire is a 23-item questionnaire that assesses insights into avoidance and maladaptive patterns; and goals and adaptive patterns (Davis 2021b).
- The Monitor Rating Form is used by the therapists present during the dosing session to provide ratings at different time points, including during/within the dosing session, the day after the dosing session, and at follow-up (i.e., monitor rating of enduring effects).

8.2.2.4. Qualitative (Written) Assessment

Participants will be asked to write a narrative describing their experience of the TRP-8802 sessions (i.e., Visits 5 and 8) before their next in-person meeting. This narrative description will be discussed at the integration sessions, and will also be used in qualitative analyses to investigate common themes associated with this therapy in the context of FM. In addition, participants will be asked open-ended questions at Visit 14 to gauge persistent changes in behavior, thought patterns, and emotions related to the TRP-8802-assisted therapy.

8.2.2.5. Self-Pain Enmeshment

The enmeshment of the "self" and "pain" will be assessed by the Pictorial Representation of Illness and Self Measure (PRISM) (Paschali et al., 2021). PRISM can be conducted via paper or digitally on a computer using commercial software (https://prismium.ch/en/get-to-know-prism.html).This task involves participants defining how they perceive themselves in relation to their experience of pain. To illustrate this relationship, the self and one's pain condition are represented by circles on a flat surface like a piece of paper or a computer screen. Participants are asked to imagine that the background surface represents their life and that one of the circles symbolizes their concept of self. They will then be given another circle and asked to imagine that it represents their pain, positioning this pain circle in a location relative to the "self" circle that best reflects the importance or intrusiveness of pain on their life.

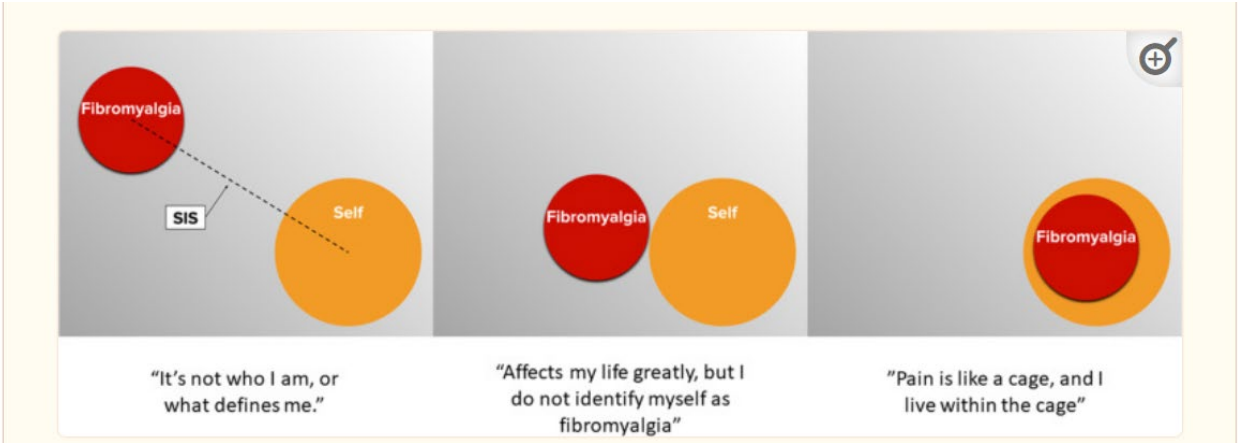


Figure 2. Examples of the Pictorial Representation of Illness and Self Measure (PRISM), with the red "pain" circle (fibromyalgia) and the yellow "self" circle. Adapted from Paschali et al., 2021.

[Note: When conducted via paper, the circles are operationalized by pieces of paper cut into circular disks that can be moved around on flat sheet of paper.] The outcome metric, called self-illness separation (SIS), is the numerical distance between the circles and represents how much pain is intertwined with their concept of self.

8.2.2.6. Self-Complexity Task.

Participants are given a stack of randomly ordered index cards, each containing the name of a descriptor (trait) from the list below (Table 5), along with a blank sheet of paper divided into vertical columns. The task is to group the traits that they believe go together, with each group representing an aspect of the patient or their life. They are free to create as many stacks of cards as they wish, and each stack can have as many or as few traits as desired. Participants do not have to use all the cards, and they can also use each card multiple times if needed. Once they form the stacks, they are asked to write down the index number of each trait card in the respective column on the blank paper, with each column dedicated to each of the stacks of cards the patient has formed. The outcome is the number of columns used/groups formed, and the number of traits in each.

Table 5. The Self-Complexity Trait List.

Accepting	Resentful	1.
Outgoing	Shy	2.
Courageous	Fearful	3.
Independent	Dependent	4.
Organized	Unorganized	5.
Empathetic	Selfish	6.
Creative	Unimaginative	7.
Sensible	Impulsive	8.
Adaptable	Rigid	9.
Honest	Manipulative	10.
Smart	Stupid	11.
Energetic	Fatigued	12.
Confident	Insecure	13.
Resilient	Helpless	14.
Self-Reflective	Confused	15.
Focused	Unfocused	16.
Assertive	Passive	17.
Easygoing	Tense	18.
Hardworking	Irresponsible	19.
Optimistic	Pessimistic	20.
Compromising	Aggressive	21.
Happy	Grieving	22.
Patient	Impatient	23.
Open-minded	Closed-minded	24.
Humorous	Guilty	25.

8.2.2.7. Expectations assessment

Participants will complete the 10-item Stanford Expectations of Treatment Scale (SETS) (Younger 2012) to assess participant expectations of outcomes associated with this treatment. This scale asks participants to rate whether they think the treatment will be effective, their worries about their condition, whether their condition will be resolved after treatment, and fears, confidence, and nervousness about the treatment.

8.2.3. Study Personnel Reported Outcomes (Exploratory Endpoints)

8.2.3.1. Quantitative Sensory Testing

The Quantitative Sensory Testing (QST) behavioral session will have the effect of rendering participants non-naïve to the experimental conditions in the imaging session, an aspect that might be argued to have some impact on the imaging results (particularly with regard to brain activity underlying cognitive and emotional functions). Advantages of this session include: identification of individuals with unstable ratings; a thorough training in the use of the rating scales; and the reduced potential for developing experiment-related anxiety and head motion in the imaging session. All QST procedures have been evaluated for safety and are well tolerated by chronic pain patients (Petersen 2015, Goodin 2009, Weissman-Fogel 2009, Price 2002).

Cuff Pressure Pain

Large volume, deep muscle pressure sensitivity (Graven-Nielsen 2015, Izumi 2014) will be assessed using an MRI-compatible rapid cuff inflator (Hokanson, Bellevue, WA) (Loggia 2012, Polianskis 2002, Polianskis 2001). This system includes an air compressor, computerized pressure controller, and a 13.5 cm by 82.5 cm Velcro-adjusted pressure cuff. Participants will first receive an ascending series of cuff pressures, starting at 20 mm Hg to 40 mm Hg and increasing in 20 mm Hg steps (10 second pressures, 20 second intervals) to tolerance or a maximum of 400 mm Hg. Each pressure will be rated after deflation on a 0 to 100 NRS. These pain ratings will be used to interpolate a series of eight tolerable cuff pressures that will be delivered in pseudo-randomized order and rated individually on pain intensity and unpleasantness. Stimulus response curves will be constructed for each participant and used for analysis, along with several derived variables: cuff-PPT, cuff-Pain50, and cuff-tolerance. In addition, tonic pain induced by continuous cuff pressure will be assessed (tonic-cuff). Each participant's individually calibrated Pain40-60 pressure (i.e., pressure that evokes a 40 to 60/100 pain rating) will be applied for 6 to 8 minutes to one gastrocnemius muscle. Pain intensity and unpleasantness ratings will be obtained every 60 seconds. This tonic cuff procedure will also be performed during fMRI.

Visual Hypersensitivity Assessment

In addition to hypersensitivity to painful stimuli applied to the body, many people with chronic pain report hypersensitivity to nonpainful sensory stimuli, including to auditory, olfactory, and visual stimulation (Lopez-Sola 2014, Wilbarger 2011, Geisser 2008), suggesting a global state of multisensory amplification in centralized pain. To measure non-somatic sensitivity, we will present to each participant a series of nonpainful yet aversive visual stimuli (Harte 2016). This 10 minute task consists of different visual stimuli presented in an alternating block design. The control stimulus is a fixed crosshair centered in the middle of a solid color background or a black

screen, whereas experimental stimulus is a flashing annulus checkerboard. Participants will view the stimuli on a calibrated HD radiological LCD monitor. The visual stimulus will be delivered in ascending and random order, adjusted to varying degrees of frequency (checkerboard flashing only), color, shape, motion, and/or brightness level, and rated on an NRS of sensory intensity and unpleasantness. To avoid possible AEs in vulnerable patients, this visual stimulation task will not be performed if the participant has a history of photo-induced migraines or seizures. These participants will still be allowed to complete all other procedures.

8.2.3.2. Functional Magnetic Resonance Imaging

Note: Participants who undergo MRI will meet all institutional guidelines and safety measures for MRI (e.g., no metal in the body, no claustrophobia, etc…).

The MRI sessions may include the following:

- structural MRI
- resting fMRI
- proton magnetic resonance spectroscopy (^{1}H-MRS) in the right anterior insula
- fMRI with tonic cuff pressure evoked experimental pain

Functional neuroimaging will include blood oxygenation level dependent (BOLD) fMRI at 3T using a T2*-weighted gradient echo sequence on a General Electric MR750 Discovery MR system with a 32-channel head coil (University of Michigan Functional MRI Laboratory). The entire imaging session will take no more than 1 hour in total. Familiarization procedures will be completed prior to fMRI to reduce anxiety. Participants will be instructed that the neuroimaging can be stopped at any time if a procedure becomes unbearable. The fMRI assessment should take a total of approximately 55 minutes to complete and may include any of the assessments included in Table 6.

Table 6. Proposed Overview of Neuroimaging Visit fMRI Procedures

Event	Duration (mins)
Structural	6
Resting state fMRI (eyes open) – five 5-minute scans	25
^{1}H-MRS anterior insula (right)	5
Tonic cuff fMRI (eyes open) – left side – two 5-minute scans	10
^{1}H-MRS anterior insula (right)	5

^{1}H-MRS=proton magnetic resonance spectroscopy; fMRI=functional magnetic resonance imaging

Functional Connectivity Magnetic Resonance Imaging

Functional connectivity MRI (fMRI) focuses on the default mode network (DMN) and salience network (SLN). The DMN is a constellation of brain regions engaged in self-referential cognition, which are "deactivated" during externally focused tasks (Buckner 2007, Fox 2007). Patients with more centralized pain display increased connectivity between the DMN and the insula (an SLN region [Menon 2015]) which is diminished with successful treatment (Napadow 2012). Whole-brain BOLD functional images will be acquired on the same 3 Tesla GE scanner described above, using a T2* weighted echo-planar sequence. Parameters will be: TR/TE

2040/30msec, flip angle=77°, FoV=240 mm, 33 AC-PC aligned slices, thickness 2.9 mm. Participants will rest comfortably in the scanner with eyes open for 25 minutes at the beginning of the scan session to obtain baseline measures of functional brain connectivity. Participants will be asked about current levels of pain intensity, fatigue and anxiety before and after resting state runs. Participants will also undergo two fMRI scans with tonic cuff pressure pain to evaluate functional brain connectivity response to deep pain. Pressure intensity will be set to each participant's Pain 30 to 50 level, as determined during the behavioral visit, and applied for 5 minutes for each scan. The pressure level from the behavioral visit will be verified prior to the scan initiation and re-calibrated in the event that it evokes more or less pain than anticipated. Pain intensity and unpleasantness ratings will be obtained at certain intervals during the test, up to three times and following stimulus presentation.

Pre-processing and Analyses of fMRI

Data will be quality checked, pre-processed using fMRIPrep (version 1.1.8) running on the high-performance computing resources at the University of Michigan. Briefly, preprocessing steps include physiological noise removal (RETROICOR), motion correction, realignment, co-registration, normalization to standard Montreal Neurological Institute (MNI) template, regression of nuisance variables (CompCor, motion parameters), and spatial smoothing (FWHM Gaussian kernel of 8 mm), and analyzed using Statistical Parametric Mapping (SPM)12 running under Matlab R2017a (Mathworks, Sherborn, MA, USA). The first 5 images will be discarded from the data set and not used for further analysis in order to correct for equilibration effects.

Dual Regression Independent Component Analysis Approach

The within-participant resting and cuff pain fMRI data analysis will be performed using the Group Independent Component Analysis (ICA) of fMRI Toolbox (GIFT) (Calhoun 2004). Intrinsic brain networks will be identified and quantified as component estimates. These components will then be validated using ICASSO software (Himberg 2004) for 10 iterations to ensure the reliability of ICA algorithm and to increase the robustness of the results. The number of independent components (networks) will be limited to 20 to 25 to minimize splitting into subcomponents. Participant-specific spatial maps and time courses will then be back reconstructed using spatio-temporal regression or dual regression options available in the toolbar, which ultimately creates a best approximation for each individual participant-specific Z-score component map. These Z-values reflect the degree of connectivity between each voxel and the group averaged time course of the component. To assure accuracy or know resting state networks, component maps will be identified with a spatial correlation using templates provided by previously published work (Smith 2009, Beckmann 2005). Individual resting state network maps will then be passed onto group second level analyses in SPM. Group analyses will be performed to evaluate intrinsic brain connectivity differences pre- and post-TRP-8802 treatment, how this intrinsic connectivity covaries with spontaneous pain intensity, and how networks differentially change following TRP-8802 treatment. The results will be thresholded at $p < 0.001$ voxelwise and $p < 0.05$, cluster-corrected for multiple comparisons.

Seed-voxel Functional Connectivity Approach

A complementary approach to evaluate intrinsic connectivity involving seed-voxels from distinct brain regions will be performed using the functional connectivity "CONN" toolbox (Cognitive and Affective Neuroscience Laboratory, Massachusetts Institute of Technology, Cambridge,

USA), version 15, running on Matlab R2017a (Whitfield-Gabrieli 2012). Pre-processed fMRI data from each participant are entered into the toolbox along with seed-voxel regions of interest, where time-series from each seed is extracted. White matter, cerebrospinal fluid (CSF) signal, and motion parameters are entered into the analysis as covariates of no interest. A band pass field (frequency window: 0.01 Hz to 0.1 Hz) will be applied in order to remove linear drift artifacts and high frequency noise. First level analyses will be performed by correlated seed-voxel signal with voxel signal throughout the whole brain, thereby creating seed region to voxel Fisher transformed r to z connectivity maps for each time point. These connectivity maps will be passed on to group level analysis and analyzed similar to those described in the Dual Regression ICA Approach section. While this approach can yield more focused inferences, there is some bias in choice of exact seed location and contour (Cole 2010). Thus, seeds will be carefully chosen based on the results of the evoked pain fMRI scan, with particular focus on insular clusters.

^{1}H-MRS Acquisition and Processing

^{1}H-MRS provides metrics amenable to longitudinal studies. High-resolution anatomical scans isolate identical brain structures within individuals over time thus minimizing error that otherwise would occur because of slight differences in voxel location from one evaluation to the next. Previous ^{1}H-MRS studies have utilized this approach to examine changes in the levels of central nervous system metabolites in test-retest studies (Evans 2010). ^{1}H-MRS will be focused on the right posterior insula cortex both prior to and following evoked cuff pressure pain. The right and left sides of the brain are chosen, as this these areas have been shown to be involved in chronic FM pain (Harris 2009, Harris 2008). ^{1}H-MRS studies will be performed on the same 3 Tesla GE system as for fMRI. Details of the ^{1}H-MRS methods are presented in previously published work (Harris 2009, Harris 2008). Single voxel MRS will be performed on the right anterior insula with a voxel size of 2 x 3 x 3 cm. The ^{1}H-MRS scanning protocol will be PRESS TR/TE=2000/35 ms with and without water suppression with 64 averages and a total scan time of approximately 5 minutes. The water signal will be recorded using 8 averages (scan time 16 seconds). Participants will be at rest during the ^{1}H-MRS session.

The raw data will undergo manual post-processing using ^{1}H-MRS software (LCModel; Stephen Provencher, Oakville, Ontario, Canada). LCModel uses a linear combination of individual spectra obtained from pure molecular species to fit the experimental spectra (Provencher 2001). Values for Glx (glutamine+glutamate) will be calculated as ratios to total creatine as well as absolute concentrations using the water signal for normalization. Resulting metabolite absolute concentrations will be reported in arbitrary institutional units. Since the voxels used incorporate CSF, and the volume of CSF dilutes ^{1}H-MRS-derived metabolite values, metabolite levels for CSF volume for each participant will be corrected as reported previously (Harris 2009). Voxel Based Morphometry, a toolbox that operates within the image analysis program SPM, Functional Imaging Laboratories, London, UK) will be used.

Feasibility of ^{1}H-MRS Approach

All of the ^{1}H-MRS procedures outlined above have been successfully implemented (Mawla 2021, Harris 2009, Harris 2008). These studies suggest that changes in Glx and gamma aminobutyric acid (GABA) within the posterior and anterior insula are strongly correlated with improvements in pain, with reductions in clinical pain being associated with lower Glx and higher GABA levels.

8.2.3.3. Wrist Actigraphy

Wrist actigraphy is a method of longitudinal sleep tracking in the ambulatory environment. Wrist actigraphy via the Fitbit Charge 5 or Actiwatch Spectrum (Philips Respironics) will be used. Actigraphy will be conducted among all participants to identify changes in sleep associated with TRP-8802 and psychotherapy treatment.

Objective measures of total sleep time (sleep duration), wake after sleep onset (sleep continuity), and sleep timing (sleep onset and wake time) will be assessed with wrist actigraphy. Participants will be trained to use actigraphic devices and will also complete a sleep log (0 to 10 NRS daily sleep quality, time in bed, number of wake times, final wake time, estimated sleep onset) via the actigraphic device as well as a paper diary every morning during actigraphy for additional validation (Burgess 2010a, Burgess 2010b). Data extraction, cleaning, and analysis will be performed using the proprietary algorithm provided by the manufacturer.

8.3. Other Safety Assessments

8.3.1. Electrocardiograms

For screening purposes only, a single 12-lead ECG will be obtained at the Screening visit using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Participants will be supine and rested for approximately 5 minutes before the ECG is recorded.

Screening ECGs will be read locally by the Principal Investigator for determination of meeting study entry criteria.

8.3.2. Pregnancy Testing

A urine pregnancy test will be performed, and results will be determined locally. Pregnancy test results must be negative at Screening, before TRP-8802 is administered on drug session days, and before fMRI is performed.

8.3.3. Urine Drug and Breath Alcohol Testing

The urine drug screen will be performed locally to detect tricyclic antidepressants, amphetamines, methamphetamine, MDMA (ecstasy), phencyclidine, barbiturates, benzodiazepines, cocaine, cannabis, and opioids, including opiates, oxycodone, and methadone. A breathalyzer will be used to estimate the blood alcohol content.

At Screening, participants who test positive for cocaine, methamphetamine, or opioids will be excluded from the study.

On drug session days, drug (excepting cannabis) and alcohol test results must be negative (blood alcohol content of less than 0.02% [verified with a second test]) before TRP-8802 is administered. If a participant does not have a negative result, they will be given a chance to reschedule (within the allowed window). A second failure will result in the participant's study termination.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 2, Section 10.2.1 and Section 10.2.2, respectively. Adverse event grading will be performed using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (US FDA Guidance for Industry 2007).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (Section 7). During dosing sessions, manifestations of the psychedelic experience will not be recorded as AEs unless judged by the therapists to exceed the intensity and/or duration of expected reactions.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the Baseline visit until the EOT visit, at the time points specified in the SoA (Section 1.3). Medical occurrences that begin before Baseline deep phenotyping but after obtaining informed consent will be recorded as Medical History, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 2, Section 10.2.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Recording and Follow-up of AE and/or SAE (Appendix 2, Section 10.2.3 and Section 10.2.4).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event

is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 2, Section 10.2.3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and investigator(s).
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the TRP-8802 IB or state other documents and will notify the IRB, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

8.4.5. Pregnancy

- Details of all pregnancies in female participants and in female partners of male participants will be collected for the duration of active intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner).
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner of a male participant will be followed until the end of pregnancy, either live birth or termination, to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

8.5. Clinical Safety and Monitoring

At enrollment, potential participants will be appropriately screened for exclusionary psychiatric conditions, medical co-morbidities, and concomitant medications. In addition medical screening will include blood tests including complete blood count (CBC), comprehensive metabolic panel (CMP), urine drug screen (UDS). Subjects with any clinically significant lab abnormalities will be excluded from participation.

Throughout the entire study, suicidal ideation will be assessed during every in-person visit using the C-SSRS and clinical assessment during participant interviews. Significant suicidal ideation is endorsed on items 4 or 5 on the C-SSRS. If the patient screens positive on the C-SSRS at any time during the study, they will undergo a more detailed suicidal risk assessment by study clinician. If they are determined to be at risk of suicide they will be transferred to ED for further Psychiatric evaluation.

During administration, heart rate and BP will be assessed before TRP-8802 capsule administration and at 30, 60, 90, 120, 180, 240, 300, and 360 minutes after capsule administration. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones). If a patient's blood pressure is >200 systolic or >110 diastolic for more than 15 minutes (i.e. 4 consecutive readings) they will be transferred to ED whether or not they are symptomatic.

AEs will be monitored at every study visit. Study staff will also be available throughout the course of the study for emergent AEs. Throughout the administration period, therapists will assess the presence and intensity of participant behaviors, symptoms, and non-verbal cues, which includes questions about the presence/intensity of behaviors, signs, and reported symptoms, such as peacefulness, yawning, nausea/vomiting, quantity of speech, anxiety, sleepiness, crying, restlessness, visual changes, euphoria, and feelings of unreality. They will also complete assessments of mood and safety at the end of the administration sessions.

The session therapists are trained to reassure the participants if they experience acute anxiety, agitation, paranoia, or panic. However, in the unlikely event that those symptoms do not respond to reassurance, or if a participant experiences a severe AE outside of the expected challenging experiences associated with psilocybin therapy, one of the session therapists will contact the on-call study physician. The study physician will use their clinical judgment to determine the most appropriate medical intervention. There will be an automated external defibrillator located on site and a crash cart containing medicine and equipment for emergency resuscitation, including rescue medication as described in section 6.8.1. After dosing sessions, participants will be discharged only if they meet all criteria in section 6.1.2., including being accompanied home by a responsible friend or family member.

During the post-dosing period (visits 6, 7, 9, 10), monitors will also complete assessments of participant mood and safety after therapy visits.

8.6. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.7. Genetics and/or Pharmacogenomics

Genetics and/or pharmacogenomics are not evaluated in this study.

8.8. Biomarkers

Neurophysiologic biomarkers being evaluated in this study include fMRI (Section 8.2.3.2).

8.9. Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.10. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The objective of this study is to evaluate the safety of oral TRP-8802 in concert with psychotherapy among adult participants with FM. Based on previous studies with psilocybin in other conditions (Davis 2021a, Carhart-Harris 2016), it is hypothesized that oral TRP-8802 in concert with psychotherapy will be safe and well-tolerated among participants with FM.

9.2. Sample Size Justification

The study is intended to gather preliminary evidence of safety of TRYP-8802 in conjunction with psychotherapy in participants with FM, and to help inform future clinical studies. As this is a pilot study, the sample size was selected based on previous pilot studies of psilocybin-assisted therapy in other conditions (e.g., major depression disorder) (Davis 2021a, Carhart-Harris 2016). Accordingly, for this pilot, proof-of-concept study, participants will be screened with the goal of enrolling approximately 10 participants who will complete both doses of TRP-8802 and the primary and secondary outcome measures, and complete the study and follow-up periods.

Note: "Enrolled" means a participant's agreement to participate in the clinical study following completion of the informed consent process and all screening assessments successfully. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

9.3. Analysis Sets

The following analysis populations have been defined for this study: Safety Population, Full Analysis Set Population (FAS), and Per Protocol (PP) Population. For this analysis, the definitions are presented in Table 7.

Table 7. Populations for Analysis

Analysis Set	Description
Safety Population	All participants who are enrolled, and for whom study intervention is initialized under the study protocol. Participants who do not receive any amount of the study drug will still contribute to the safety analysis if study intervention was initialized but not completed, since all AEs of intervention must be assessed. All safety analyses will utilize the Safety Population.
Full Analysis Set Population	All participants who receive 2 doses of study drug, and who have any post-baseline clinical assessments. The secondary efficacy analyses will be performed using data from the FAS Population.
Per Protocol Population	The subset of the FAS Population who complete 4 weeks of follow up post second dose with no major protocol deviations (including but not limited to: failure to satisfy all inclusion and exclusion criteria, failure to adhere to all protocol-required restrictions and prohibitions, receipt of prohibited concomitant procedures or therapies, and non-compliance to protocol-specific procedures) as determined by a review of participant data. The analysis of efficacy performed using data from the PP Population will be considered supportive of the FAS analysis.

AEs=adverse events; FAS=Full Analysis Set; PP=Per Protocol

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized and approved prior to the database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

All descriptive statistical analyses will be performed using SAS (Version 9.4 or higher) or R (Version 3.6.2 or higher), unless otherwise noted. For categorical variables, the number and percentage within each category of the parameter will be calculated. For continuous variables, the number of participants with no missing data (n), mean, median, standard deviation (SD), minimum, and maximum values will be presented.

For the purpose of statistical analyses, a month is considered equivalent to 30 days, and a year is considered equivalent to 365 days.

9.4.2. Primary Endpoints (Safety)

The safety of treatment with TRP-8802, which is evaluated by vital signs (HR and BP) and AEs, is the primary endpoint. Vital signs and AEs will be collected from the Baseline (deep

phenotyping) visit until the EOT visit (Day 64) at the time points specified in the SoA (Section 1.3).

Descriptive statistics will be used to present the count and the percentage of participants in the Safety Population who experience an AE.

9.4.3. Secondary Endpoints (Efficacy)

The results of secondary endpoints will be shown at the baseline and each follow up visits based on Full Analysis Set Population and the PP Population. Pain score, pain interference, sleep disturbance, chronic pain acceptance, and the patient global impression of change were chosen as secondary measures given their relevance to FM symptom management (Clauw 2014; Williams 2011; Kratz 2007; Farrar 2001).

Aggregate worst pain score change from baseline to EOT (Day 64) will be measured on the 11-item PI-NRS. Average daily pain score will be measured from Day 1 to 7 (baseline) versus the 7 days immediately before EOT (Days 57 to 63). Changes in the worst pain intensity from the baseline through EOT will be presented in Full Analysis Set Population and the PP Population. A 30% or 2-point decrease in aggregated worst pain scores at either movement or rest will be considered a clinically significant response (Farrar 2001).

Pain interference is the degree to which pain affects important aspects of an individual's life, such as social, cognitive, and physical activities. The pain interference and its change from the baseline will be shown at the baseline and each follow up visit. Sleep disturbance includes assessment of sleep quality, perceived ability to fall and stay asleep, satisfaction of sleep, and depth of sleep. Sleep disturbance and its change from the baseline will be reported as well. In addition, chronic pain acceptance will be presented at baseline and follow up. Finally, patient impression in clinical status change will be shown.

9.4.4. Exploratory Endpoints (Efficacy)

Exploratory endpoints may be used for possible future investigation(s) and are further described in the SAP.

9.4.5. Handling of Missing Data

Every effort will be undertaken to limit premature discontinuations and ascertain completeness of data collection. All other analyses will utilize only actual participant data which is collected; no imputation of missing data will be performed unless there is > 10% of data missing.

9.4.6. Subgroup Analysis

Due to small sample sizes, there no subgroup analyses are planned in this study.

9.5. Interim Analysis

No interim analysis is planned.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, TRP-8802 IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
  - Providing oversight of the conduct of the study at the site and adherence to the IRB and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. These data may be shared in this form with other research collaborators after completion of appropriate data sharing agreements via the University of Michigan.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5. Safety Review Committees Structure

The SRC will be responsible for the assessment of safety and to make recommendations regarding study progression. The SRC will be composed of the principal investigator, a study therapist, and a study physician. Participant safety, which includes safety signal detection at any time during the study, will be continuously monitored by the SRC. All safety data collected will be summarized and reviewed by the SRC for agreement of next steps.

In particular, data will be reviewed by the SRC if one of the following Stopping Rules is met (Section 5.5):

- one SAE considered at least possibly related to the study drug
- one Grade 3 or Grade 4 AE considered at least possibly related to the study drug
- clinically similar Grade 2 AEs considered at least possibly related to the study drug in 2 participants
- HPPD

10.1.6. Dissemination of Clinical Study Data

This study will be registered at ClinicalTrials.gov, and results from this study will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on CRFs unless transmitted to the sponsor or designee electronically (e.g., questionnaire data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the reference section of the EDC system.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 7 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Case report form data that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. The study site will be closed upon study completion. The study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of the study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRB, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings.
- Study participants shall not be identified in any publication or presentation; only study identification numbers shall be used. If photographs are to be used as illustrations, separate informed consent shall be obtained for this purpose, and photographs shall be rendered anonymous.

10.2. Appendix 2: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse. • HPPD – see Section 2.3 for definition.

10.2.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Tryp-8802 IB in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data within 24 hours of receipt of the information.

10.2.4. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- If the electronic system is unavailable, then the site will email a scanned copy of a completed paper AE CRF within 24 hours.
- If a paper copy of the AE CRF is unavailable, the site will email the Sponsor's designee to report the subject number, SAE term, and relationship of the event to the investigational product. Email contact information for reporting SAE data when the electronic data collection tool is unavailable will be provided to the site during the Site Initiation Visit.
- Initial notification of an SAE via telephone does not replace the need for the investigator to complete the AE CRF within the designated reporting time frames.
- After the study is completed at the site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated information on a previously reported ongoing SAE deemed related to the study intervention after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) directly to the Sponsor.
- Contacts for SAE reporting will be provided during the Site Initiation Visit.

SAE Reporting to via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Safety Associate.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting will be provided during the Site Initiation Visit.

10.3. Appendix 3: Abbreviations and Definitions

Term	Definition
^{1}H-MRS	proton magnetic resonance spectroscopy
5-HT	5-hydroxytryptamine
ΔHR	change in heart rate
AE	adverse event
BOLD	blood oxygen level dependent
BP	blood pressure
CFR	Code of Federal Regulations
CPAQ-8	Chronic Pain Acceptance Questionnaire 8
CRF	case report form
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DMN	default mode network
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	electrocardiogram
EDC	electronic data capture
EOT	end of therapy
FAS	Full analysis set
FDA	(United States) Food and Drug Administration
FM	fibromyalgia
fMRI	functional connectivity magnetic resonance imaging
GABA	gamma aminobutyric acid
GLM	general linear model
Glx	glutamine+glutamate
HIPAA	Health Insurance Portability and Accountability Act
HPPD	hallucinogen persistent perception disorder
HR	heart rate
IB	Investigator's Brochure
ICA	Independent Component Analysis
IRB	Institutional Review Board
MDMA	3,4-methylenedioxy-methamphetamine
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
PANAS	Positive and Negative Affect Schedule
PGIC	Perceived Global Impression of Change
PHQ-8	Patient Health Questionnaire depression scale
PI-NRS	Pain Intensity-Numeric Rating Scale

Term	Definition
PK	pharmacokinetics
PP	per protocol
PRN	pro re nata translated as needed
PROMIS	Patient Reported Outcomes Measurement Information System
PROMIS29+2	Patient Reported Outcomes Measurement Information System 29-item profile measure plus 2 cognitive functioning items
QST	Quantitative Sensory Testing
QTLs	quality tolerance limits
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCID-5	Structured Clinical Interview for DSM-5
SCID-5-PD	Structured Clinical Interview for DSM-5 for Personality Disorders
SLN	salience network
SoA	Schedule of Activities
SPM	Statistical Parametric Mapping
SRC	Safety Review Committee
TRP-8802	psilocybin drug substance prepared according to current manufacturing processes at Usona Institute, which is supplying study drug

11. References

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